PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/003061	22.03.2005	23.03.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/48

Applicant
COMPLEX BIOSYSTEMS GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

González Ramon, N.

Telephone No. +31 70 340-3466

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/003061

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3, 5-9, 14-19, 26, 37-39, 73 complete; 1,2,4,10-13,20-25,27-36,40-72,74-88 in part

because:

☒ the said international application, or the said claims Nos. 76-88 in relation to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 3, 5-9, 14-19, 26, 37-39, 73 complete; 1,2,4,10-13,20-25,27-36,40-72,74-88 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1,2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 in part

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,2,4,10-13,20-25,27-36,40-72,74-88
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,2,4,10-13,20-25,27-36,40-72,74-88
Industrial applicability (IA)	Yes:	Claims	1,2,4,10-13,20-25,27-36,40-72,74, 75
	No:	Claims	76-88 see separate sheet

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/003061

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

"copolymers, grafted copolymers, cross-linked polymers and block copolymers from the above listed" (claim 13); "an activating agent" (claim 42); "a protecting group" (claims 41, 49, 55, 58, 60, 64-67).
In fact, the claims contain so many options, variables and possible permutations that a lack of clarity within the meaning of Article 6 PCT arises.

Moreover claims relate to an extremely large number of possible chemical groups defined by vague characteristics or properties, namely: "derivatives" (claims 22, 23). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the chemical groups claimed. Again the claims lack support, and the application lacks disclosure.

Furthermore claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function have not been defined, namely "amine containing biologically active moiety", "a leaving group", " a nucleophile" (claims 1, 2, 40, 42, 45, 50, 53, 60, 63); "activating agent" (claim 42); "central nervous system active agent, anti-infective, anti-neoplasic, antibacterial, anti-fungal, analgesic, contraceptive, anti-inflammatory, vasodilating, vasoconstricting, cardiovascular agent", (claim 10); "protecting group" (claims 41, 49, 55, 58, 60, 64-67).

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.
Therefore, claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 do not fulfil the requirements of Art. 5 and Art. 6 PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 76-88 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT:

Present claims 1, 2, 4, 10-13, 20-24, 27-36, 40-72, 74-88 as far as related to the first invention relate to an extremely large number of possible compounds defined as "amine containing biologically active moiety", "any heteroatom containing a free electron pair", "a leaving group", " a nucleophile" (claims 1, 2, 40, 42, 45, 50, 53, 60, 63); "a small molecule (claim 4); "central nervous system active agents", "anti-infective", "anti-neoplastic", "antibacterial", "anti-fungal", "analgesic", "contraceptive", "anti-inflammatory", "steroidal", "vasodilating", "vasoconstricting", "cardiovascular agents with at least one primary or secondary amino group" (claim 10); "substituted or non substituted linear, branched or cyclical alkyl or heteroalkyl", "substituted aryl", "substituted or non substituted heteroaryl", "carboxylakyl, alkylcarbonyl", "carboxamidoalkyl", "substituted or non substituted linear, branched or cyclical alkoxy", "substituted or non substituted linear, branched or cyclical heteroalkyloxy, aryloxy, heteroaryloxy", "substituted or non substituted linear, branched or cyclical heteroaryl, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl", "a polymer" (claims 1, 2, 12, 40, 41, 58, 65, 66, 68, 69); "a multi-substituted aromatic hydrocarbon", "a multi-substituted aromatic heterocycle" (claims 1, 2, 40); "other carbohydrate based polymers",

Support is only to be found in the present application for those parts relating to the compounds specifically mentioned by chemical name in the examples and in claims 11, 13, 27-36 wherein the linkers are as recited in claims 22-25 excluding the vague term "derivative" and as such has been the subject of the search.

No opinion will be formulated by the ISA in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item IV

Lack of unity of invention

The present application lacks unity of invention (Rule 13.1 PCT) for the following reasons:

The problem underlying the present invention is the interpatient variability and unpredictable effect of prodrug activation when enzymatic mechanism is involved (see page 12, lines 17-30)

As solution to this problem several molecular constructs containing an aromatic molecule linker conjugated to diverse polymers (branched, hyperbranched, dendrimers, polypeptides) and attached to the drug (small molecule, proteins, peptides, peptide nucleic acids) as well as constructs wherein the drug is not present (substituted by a leaving group A) are proposed. Methods for synthesising the compounds claimed and the intermediates used in said methods are also encompassed.

The common feature linking the different inventions together is the presence of a "self-inmolative" aromatic linker in order to trigger the liberation of the drug in an active form as presented in description page 17.

Prior art documents:

WO03057716 discloses dendritic encapsulation of peptide drugs or small molecule drugs (see page 7-8) bound to a scaffold covalently attached to the dendritic polysaccharide encompassed under polymer R1 of present application by an azide, amide, thioester,

disulfide, ester, carbonate, carbamate or ureide bonds (see claims 10, 11). Scaffolds of aglycone, nitro and azocompounds containing aromatic group (encompassed under Ar of present application) allow release mechanism based in internal cyclization (see figure 3, 5).

WO02083180 discloses multiple electronic cascade spacers wherein p-nitrophenyl carbonate is included as activating group for facilitation of coupling of the spacer with other moieties. Optionally linked to a polymer (see page 10, lines 25-28). Therapeutic moieties include anticancer drug (daunorubicin, doxorubicin, idarubucin, mitoxantrone) (see claim 13, 14).The mechanism of elimination comprises unmasking/activation followed by electronic cascade reaction 1,6 (see figures 3, 5).

WO2004019993 discloses self immolative dendrimers releasing active moieties upon cleavage activation. The mechanism of drug release from a prodrug is triggered by hydrolytic cleavage of the masking group (see page 32, lines 7-13) followed by an internal cyclization (see figure 3). Self immolative chemical linker consisting on formula IB encompassed under the aromatic linker claimed (see claims 3,7,13,16,24,123,129,161; page 5). Chemotherapeutic agents as daunorubicin, doxorubicin, anti-inflammatory, antibiotics, antiviral and anti hypertensive agents are encompassed (see page 25, line 12-page 26, line 10).

- Shabat el at, in Chem. Eur. J. (2004), vol. 10, pp. 2626-2634 disclose chemical adaptor systems encompassing aromatic linkers as prodrugs constituents (see figures 1, 2, 8). Mechanisms to release the drugs including hydrolytic trigger cleavage followed by elimination reaction or intra-cyclization reaction are described (see abstract, conclusions).

WO03026577 discloses Aminobenzylether self-immolative spacer X on a compound of formula L-(An-Z-X-Ww-)-D wherein L is a ligand comprising antibodies, enzymes, interleukins, interferons, polyethylene glycol, polypropylenglycol, hydroxypropylmethacrylamide, dextran, polyglutamic acid embraced under R1 of present claim 13, D is a drug moiety, Z is an aminoacid or peptide, A is optionally acyl unit and W is optional second self immolative group (see pages 6,7; page 16, lines 8-31; claims 37-44, 79, 93)

The idea to provide an aromatic self immolative linker is known and obvious over the prior art, and cannot serve as single general inventive concept linking the individual subjects in which the application has been divided. As there is no other technical feature which could fulfil the role of special technical feature in the sense of rule 13 PCT, the present application lacks unity of invention, containing the following subjects.

1. Claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a polymer as recited in claim 13 and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 2-31

2. Claims 1, 2, 4-9, 12, 13, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a polymer as recited in claim 13 and T is protein or polypeptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1, 3-31

3. Claims 1, 2, 4, 5, 12, 13, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a polymer as recited in claim 13 and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1, 2, 4-31

4. Claims 1, 2, 4, 10-12, 14, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is an hydrogel and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-3, 5-31

5. Claims 1, 2, 4-9, 12, 14, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a hydrogel and T is a protein or peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject

matter of inventions 1-4, 6-31

6. Claims 1, 2, 4, 5, 12, 14, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is an hydrogel and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-5, 7-31

7. Claims 1, 2, 4, 10-12, 15, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a branched or hyperbranched polymer and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-6, 8-31

8. Claims 1, 2, 4-9, 12, 15, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a branched or hyperbranched polymer and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-7, 9-31

9. Claims 1, 2, 4, 5, 12, 15, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a branched or hyperbranched polymer and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-8, 10-31

10. Claims 1, 2, 4, 10-12, 16, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a dendrimer or dense star polymer and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-9, 11-31.

11. Claims 1, 2, 4-9, 12, 16, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a

dendrimer or dense star polymer and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-10, 12-31

12. Claims 1, 2, 4, 5, 12, 16, 20-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a dendrimer or dense star polymer and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-11, 13-31

13. Claims 1, 2, 4, 10-12, 17-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a biopolymer or a protein and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-12, 14-31.

14. Claims 1, 2, 4-9, 12, 17-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a biopolymer or protein and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-13, 15-31

15. Claims 1, 2, 4, 5, 12, 17-25, 27-36, 40-72, 74-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 2 wherein R1 is a biopolymer or a protein and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-14, 16-31

16. Claims 1, 3, 4, 10-13, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a polymer as recited in claim 13 and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-15, 17-31

17. Claims 1, 3-9, 12, 13, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a polymer as recited in claim 13 and T is protein or polypeptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-16, 18-31

18. Claims 1, 3-5, 12, 13, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a polymer as recited in claim 13 and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-17, 19-31

19. Claims 1, 3, 4, 10-12, 14, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is an hydrogel and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-18, 20-31

20. Claims 1, 3-9, 12, 14, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a hydrogel and T is a protein or peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-19, 21-31

21. Claims 1, 3-5, 12, 14, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is an hydrogel and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-20, 22-31

22. Claims 1, 3, 4, 10-12, 15, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a branched or hyperbranched polymer and T is a biologically active small molecule.

Excluding the subject matter of inventions 1-21, 23-31

23. Claims 1, 3-9, 12, 15, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a branched or hyperbranched polymer and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-22, 24-31

24. Claims 1, 3-5, 12, 15, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a branched or hyperbranched polymer and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-23, 25-31

25. Claims 1, 3, 4, 10-12, 16, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a dendrimer or dense star polymer and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-24, 26-31

26. Claims 1, 3-9, 12, 16, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a dendrimer or dense star polymer and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-25, 27-31

27. Claims 1, 3-5, 12, 16, 20-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a dendrimer or dense star polymer and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-26, 28-31

28. Claims 1, 3, 4, 10-12, 17-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a

biopolymer or a protein and T is a biologically active small molecule. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-27, 29-31

29. Claims 1, 3-9, 12, 17-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a biopolymer or protein and T is a protein or a peptide. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-28, 30-31

30. Claims 1, 3-5, 12, 17-25, 27-36, 40-88 in part
Polymeric cascade prodrug having the structure as depicted by claim 3 wherein R1 is a biopolymer or a protein and T is an oligonucleotide or peptide nucleic acid. Method of administration of the same comprising cleavage from the carrier by means of a non-enzymatic reaction. Excluding the subject matter of inventions 1-29, 31

31. Claims 26, 37-39 complete; 1-3, 12-25, 27-36, 40-52, 54, 55, 60-62, 64-71 in part
Molecule having the structure as depicted by claims 2 or 3 wherein R1 is a polymer and T is leaving group A. Excluding the subject matter of inventions 1-30

Rule 13.1 PCT requires that all the claimed alternatives have a common property or activity, and a common structure is present, i.e. a significant structural element is shared by all alternatives, or all alternatives belong to a recognised class of chemical compounds in the art to which the invention pertains. In the present case, the compounds defined by the claims allegedly share a common therapeutic activity. Each of the groups of compounds listed, represents a mere alternative characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art, which is the structurally distinctive feature of each group. There appears to be no technical relationship between the special technical features characterising the structurally different groups of compounds claimed in the present application. No further technical feature(s) can be identified which may be regarded as a special technical feature involved in the technical relationship between the different inventions.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 76-88 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The following documents (D) are referred to in this communication:

D1: WO 03/057716 A (BOERTH NANCY JOHNSTON ; NEW RIVER PHARMACEUTICALS INC (US); BISHOP BAR) 17 July 2003 (2003-07-17)
D2: WO 02/083180 A (BEUSKER PATRICK HENRY ; BUSSCHER GUUSKE FREDERIKE (NL); SCHEEREN JOHAN) 24 October 2002 (2002-10-24)
D3: WO 2004/019993 A (LIST BENJAMIN ; PESSAH NETA (IL); SHAMIS MARINA (IL); AMIR ROEY JACOB) 11 March 2004 (2004-03-11)
D4: SHABAT D. ET AL: CHEM. EUR. J., vol. 10, 22 March 2004 (2004-03-22)
D5 : WO 03/026577 A (SEATTLE GENETICS, INC; SENTER, PETER, D; TOKI, BRIAN, E) 3 April 2003 (2003-04-03)

Novelty (Art 33 (2) PCT)

The subject-matter of claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 is not new in the sense of Article 33(2) PCT. The reasons therefore are the following:

D1 discloses dendritic encapsulation of peptide drugs or small molecule drugs (see page 5, paragraph 2) bound to a scaffold covalently attached to the dendritic polysaccharide encompassed under polymer R1 of present application by an azide, amide, thioester, disulfide, ester, carbonate, carbamate or ureide bonds (see claims 10, 11). Scaffolds of aglycone, nitro and azocompounds containing aromatic group (encompassed under Ar of

present application) allow release mechanism based in internal cyclization (see figure 3, 5).
Consequently the subject matter of present claims 1, 2, 4, 10-13, 21-25, 32, 34-36, 74-88 is not novel over D1.

D2 discloses multiple electronic cascade spacers wherein p-nitrophenyl carbonate is included as activating group for facilitation of coupling of the spacer with other moieties. Optionally linked to a polymer (see page 10, lines 25-28). Therapeutic moieties include anticancer drug (daunorubicin, doxorubicin, idarubucin, mitoxantrone) (see claim 13, 14).The mechanism of elimination comprises unmasking/activation followed by electronic cascade reaction 1,6 (see figures 3, 5).
Therefore the subject matter of claims 1, 2, 4, 10-12, 20-25, 32-36, 40-72, 74-88 is not novel in view of D2.

D3 discloses self immolative dendrimers releasing active moieties upon cleavage activation. The mechanism of drug release from a prodrug is triggered by hydrolytic cleavage of the masking group (see page 32, lines 7-13) followed by an internal cyclization (see figure 3). Self immolative chemical linker consisting on formula IB encompassed under the aromatic linker claimed (see claims 3, 7, 13, 16, 24, 123, 129, 161; page 5, compound IB). Chemotherapeutic agents as daunorubicin, doxorubicin, anti-inflammatory, antibiotics, antiviral and anti hypertensive agents are encompassed (see page 25, line 12-page 26, line 10; page 32, lines 6-16).
Consequently the subject matter of present claims 1, 2, 4, 10-12, 20-25, 27-36, 40-72, 76-88 is not novel over D3.

D4 disclose chemical adaptor systems encompassing aromatic linkers as prodrugs constituents in the attachment to polymer carriers (see figures 1, 2, 8). Mechanisms to release the drugs including hydrolytic trigger cleavage followed by elimination reaction or intra-cyclization reaction are described (see abstract, conclusions).
Therefore the subject matter of claims 1, 2, 4, 10-12, 20-25, 27-36, 40-72, 76-88 is not novel in view of D4.

D5 discloses Aminobenzylether self-immolative spacer X on a compound of formula L-(An-Z-X-Ww-)-D wherein L is a ligand comprising antibodies, enzymes, interleukins,

interferons, polyethylene glycol, polypropylenglycol, hydroxypropylmethacrylamide,dextran, polyglutamic acid embraced under R1 of present claim 13, D is a drug moiety, Z is an aminoacid or peptide, A is optionally acyl unit and W is optional second self immolative group (see pages 6,7; page 16, lines 8-31; claims 37-44, 79, 93).
Consequently the subject matter of present claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 76-88 is not novel over D5.

Inventive step (Art 33(3) PCT)

Should the applicant overcome the above raised objections, an inventive step has to be demonstrated for the subject matter of present claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 as far as related to the first invention (Art 33(3) PCT).

The problem underlying the present invention is the interpatient variability and unpredictable effect of prodrug activation when enzymatic mechanism is involved (see page 12, lines 17-30)

As solution to this problem a molecular constructs containing an aromatic molecule linker conjugated to diverse polymers as listed in claim 13 and attached to the drug (small molecule) is proposed as the first invention. Methods for synthesising the compounds claimed and the intermediates used in said methods are also encompassed.

Document D4, which can be considered the closest prior art for the assessment of inventive step of the present application already addresses the preparation of chemical adaptor systems encompassing aromatic linkers as prodrugs constituents in the attachment to polymer carriers (see abstract, conclusions).
Mechanisms to release the drugs including hydrolytic trigger cleavage followed by elimination reaction identical to the ones disclosed by present application on description page 10 are described in this document (see figures 2A, 2B, 8)

Previously discussed D5 consists on equivalent document for the assessment of inventive step.

The difference between D4/D5 and the subject matter of the present application is that the

particular trigger cleavage other than by a catalytic antibody of by enzyme (thus non-enzymatic hydrolysis) as specified by claims 74, 75 is not explicitly worded in D4/D5.

Unless a surprising achievement of an improved technical effect of the particular hydrolysis step over D4/D5 is shown, such solution cannot be considered as involving an inventive step, but as providing equivalent alternatives of the hydrolysis step in order to trigger the prodrug activation which are obvious for the skilled person solely relying on known properties of known compounds.

Moreover the attention of the applicant is drawn to the fact that all embodiments covered by the claims should satisfy the criteria of inventive step. When the inventive step is solely based on the achievement of a technical effect, such as preparing a conjugate molecule as depicted in claim 2, in the present case, substantially all embodiments embraced under the functional groups defined by the claims should exhibit this effect. It must be credible that all the alternatives claimed must be a solution to the problem.

However, it is evident that the number of compounds/methods which are encompassed by claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 as defined: "amine containing biologically active moiety", "any heteroatom containing a free electron pair", "a leaving group", " a nucleophile" (claims 1, 2, 40, 42, 45, 50, 53, 60, 63); "a small molecule (claim 4); "central nervous system active agents", "anti-infective", "anti-neoplastic", "antibacterial", "anti-fungal", "analgesic", "contraceptive", "anti-inflammatory", "steroidal", "vasodilating", "vasoconstricting"; "cardiovascular agents with at least one primary or secondary amino group" (claim 10); "substituted or non substituted linear, branched or cyclical alkyl or heteroalkyl", "substituted aryl", "substituted or non substituted heteroaryl", "carboxylakyl, alkylcarbonyl", "carboxamidoalkyl", "substituted or non substituted linear, branched or cyclical alkoxy", "substituted or non substituted linear, branched or cyclical heteroalkyloxy, aryloxy, heteroaryloxy", "substituted or non substituted linear, branched or cyclical heteroaryl, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl", "a polymer" (claims 1, 2, 12, 40, 41, 58, 65, 66, 68, 69); "a multi-substituted aromatic hydrocarbon", "a multi-substituted aromatic heterocycle" (claims 1, 2, 40); "other carbohydrate based polymers", "copolymers, grafted copolymers, cross-linked polymers and block copolymers from the above listed" (claim 13); "an activating agent" (claim 42); "a protecting group" (claims 41, 49, 55, 58, 60, 64-67) is such that it is unlikely that all of them posses the effect claimed.

Therefore, as part of the subject matter of claims is not likely to exhibit this particular technical effect in a credible manner, said subject matter cannot involve inventive step

Consequently an inventive step for the subject matter of claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 cannot be acknowledged.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO20004043493	27.05.2004	14.11.2003	14.11.2002
EP1525890	27.04.2005	02.10.2003	
WO2005082023	09.09.2005	22.02.2005	23.02.2004

The PCT application WO2004/043493 published on 27.05.2004 claims the priority date of 14.11.2002.

This earlier application shows prodrugs built as multiple self-elimination aromatic release spacers encompassed by present claim 1 (see claims 5, 7), wherein p-nitrophenyl carbonate is included as activating group for facilitation of coupling of the spacer with other moieties (see page 34, lines 18-20; claim 28). Optionally linked to a polymer including polyethylene glycol, poly (glutamic acid), poly HPMA (see page 50, line 30-page 51, line 10). Therapeutic moieties include anticancer drug (daunorubicin, doxorubicin, idarubucin, mitoxantrone), antibiotic, antiinflammatory agent or antiviral agent (see page 41, line 15-page 42, line 8; example 9; claim 17).
The mechanism of elimination comprises unmasking/activation of specifier by chemical, photochemical, physical activation (see page 15 lines 1-4) followed by electronic cascade reactions of self eliminating spacers (see figures 5, 7; examples 24, 25)

Thus, it would be prejudicial to the novelty of the subject-matter of claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 of the present application.

The EP application EP1525890 published on 27.04.2005 claims the priority date of 02.10.2003.
This earlier application shows: Cleavable insulin dendrimers comprising a self immolative aromatic linker embraced under formula of present claim 2 wherein the release of the free insulin takes place by non enzymatic reaction at pH 7.4 (see page 69; pages 71-72).

Thus, it would be prejudicial to the novelty of the subject-matter of claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 of the present application.

The PCT application WO2005/082023 published on 09.09.2005 claims the priority date of 23.02.2004.
This earlier application shows: Heterocyclic self-immolative linkers and conjugates with ligands including antibodies. The linker comprises a peptide substrate for an intracellular enzyme. Upon cleavage of the peptide sequence, the selfimmolating moiety cleaves itself from the drug and liberates it in an active form (see abstract, claims 4, 5, 34, 35; figure 1).

Thus, it would be prejudicial to the novelty of the subject-matter of claims 1, 2, 4, 10-13, 20-25, 27-36, 40-72, 74-88 of the present application.